SUBCOMMITTEE ON HARMONIZATION (SOH) UPDATE

Mark Barnes
David Forster

July 20, 2011

Membership

- Susan Alpert, Ph.D, M.D.
- Mark Barnes, J.D., LL.M. - Co-Chair
- Gary Chadwick, Pharm.D., CIP (new member)
- David Forster, J.D., MA, CIP – Co-Chair
- Dean Gallant, A.B.
- Karen N. Hale, RPh, MPH, CIP
- Justin P. McCarthy, J.D.
- Marjorie A. Speers, Ph.D.
- Susan Stayn, J.D.

Meetings

- Convened meetings:
  - April 15-16, 2010.
  - September 21-22, 2010.
  - February 8-9, 2011.
  - June 29-30, 2011.
- Monthly teleconferences.

Completed Activity – HHS Conflict of Interest Policies

- Recommendation regarding adoption of a single conflict of interest standard across DHHS entities.
- Adopted by SACHRP at July 21, 2010 meeting.

Completed Activity – Comparison of Common Rule and FDA Regulations

- Reviewed differences between Common Rule FDA at SOH meeting of September 21-22, 2010.
- Many of the differences are based in unique roles of the agencies and are not problematic:
  - Differences in waivers of documentation of consent
  - FDA emergency use regulation.
- This background is informing continuing SOH activities, but no recommendation on solely this comparison is planned.

Completed Activity – Commentary on NPRM on HITECH

- Recommendation adopted by SACHRP at October 19, 2010 meeting.
- Five topics:
  - Compound Authorizations
  - Future/Secondary Research
  - Minimum Necessary
  - Business Associates
  - Restriction on Sale of PHI

Completed Activity – Definition of Non-Scientist

- Recommendation adopted by SACHRP at October 19, 2010 meeting.

Completed Activity – Review of Draft Response to the Presidential Commission

- At its last convened meeting, SOH considered the SAS draft recommendation regarding SACHRP response to the Presidential Commission's *Request of Comments on Human Subjects Protections in Scientific Studies*.
- This draft and the general issue was discussed yesterday by SACHRP.

Four Items for SACHRP's Consideration

- SOH additions to the Subpart A Subcommittee (SAS) FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens.
- Recommendation regarding definition of a Minor Change in Research.
- Recommendation regarding application of 45 CFR 46 and 21 CFR 56 to early processes in research, such as identifying potential subjects, contacting subjects, and recruiting subjects.
- Recommendation on HIPAA and Access Reports.

FAQs on Biospecimens

- SOH additions to the Subpart A Subcommittee (SAS) "FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens."
- FAQ content approved by SACHRP in July and October, 2009, and March, July and October 2010.
- SOH suggestions include addition of FDA application, additional HIPAA sections, and revisions to some existing sections.

Minor Change in Research

- Minor changes in research that can be reviewed through the expedited procedure.
- This issue has been discussed at SACHRP intermittently since March 4, 2009.
- Suggestions from SACHRP meeting of March 9, 2011 included.
- SOH requests that SACHRP approve the recommendation.

Issues at the Beginning of Research

- Recommendation regarding application of 45 CFR 46 and 21 CFR 56 to early processes in research, such as identifying potential subjects, contacting subjects, and recruiting subjects.
- Substantial differences among OCR, FDA, and OHRP regulations and guidance on this issues.
- Suggestions from SACHRP meeting of March 9, 2011 included.
- SOH requests that SACHRP approve the recommendation.

HIPAA Accounting of Disclosures and Access Reports

- Recommendation supporting HHS proposal to exempt research disclosures from the Accounting Requirement.
- Statement of concerns regarding the new proposed Access Report requirements as it applies to research.
- SOH requests that SACHRP approve the recommendation and statement of concerns.

Future Topic - Standard practice vs. Innovative care vs. research vs. clinical investigation

- QA/QI activities, especially QA/QI activities involving FDA regulated products or products that may or may not be FDA regulated (example, skin cleaner on wash cloth versus a marketed product for cleaning skin.).
- CDC definition of research vs. QI vs. epidemiology.

Future Topic - Engagement of Community in Research

- How and when should community be engaged in research.
- No clear protocol or method, subjects are involved in design.
- HPTN, HVTN, NIADA CAB utilize community participation.
- Community consultations under 50.24.

Future Topic - Consent Issues

- Use of partially translated short form for non-English speakers. OHRP versus FDA. OCR silent.
- Documentation of consent/signature requirements. HHS signature vs. FDA signature and date vs. ICH signed copy and witness signature for illiterate subjects.

Future Topic - Application of Subparts B, C, D

- Unequal application of the subparts across agencies.

Future Topic - International

- Common Rule vs. FDA vs. ICH vs. OCR.
- Also European laws, other laws around the world.
- Preemption issues.

Possible Future Topic - State laws, Non-HHS agencies

- Broadest issue, outside current focus of SOH.

Future Topic - Incapacitated Adults

- SIIIDR report.
- VA guidance.
- new FDA information sheets.
- ICH.
- OHRP FAQ on LAR.
- NIH Points to Consider.
- Could and should all these be harmonized?

Future Topic - Safety Issues

- Unanticipated problems and overall protocol safety assessment by sponsors and others.
- FDA guidance on DSMBs and NIH requirements for DSPs.
- Continuing difference between FDA and OHRP UP guidances. Mostly issue of seriousness. Could it be a single guidance?

Future Topic - Local Attitudes

- FDA versus OHRP guidance.

Future Topic - Exculpatory language

- What is exculpatory language?
- Issue mostly focused on property rights in tissues.
- FDA and OHRP working on guidance.
- ESCRO standards, state laws, DOD differ.

FDA Proposed Rule – Investigator Falsification of Data

- What needs to be reported?
  - "Sponsors would be required to report to the appropriate FDA center information indicating that any person has, *or may have*, engaged in the falsification of data" [emphasis added].
  - " 'Falsification of data' is defined…as creating, altering, recording, or omitting data in such a way that the data do not represent what actually occurred." Examples include:
    - "Creating data that were never obtained …forging the signature on an informed consent form"
    - "Altering data by re placing original data with something different that does not accurately reflect study conduct or results"
- Time frame for reporting: "Promptly, but no later than 45 calendar days after the sponsor becomes aware of the information"

Of note, we are already seeing sponsor agreements that require the institution to report

FDA Proposed Rule – Investigator Falsification of Data

- What information is required in the report?
  - "The name of the person who has, *or may have*, falsified data" [emphasis added] and identifying data, inter alia
- The proposed rule also "encourages" other persons to report such information
  - Such reports will be received directly by FDA, without knowledge of or action by institution or sponsor

Of note, we are already seeing sponsor agreements that require the institution to report

Future Topic - Procedural Issues

- Creation of a single new agency to oversee all human subjects research in the US.
- Procedural changes in the way that the common rule agencies establish guidance in order to promote harmonized guidance.
- Procedural changes to require or promote joint regulations and/or guidance from OHRP and FDA and other HHS agencies.

Current Topic – Research Misconduct

- Do any abuses of human subjects give rise to ORI-defined research misconduct violations?
- Are there research misconduct violations that are clear violations of human subjects research standards?
- Can research misconduct issues arise in FDA enforcement actions?
  - What if FDA findings, or institutional/researcher/sponsor reports to FDA, precede any final research misconduct determinations?

Research Misconduct - Examples

- Researcher systematically varies protocol from what was presented to and approved by IRB, and publishes results; later analysis reveals that results were rendered unreliable by the non-compliance, and publication is withdrawn
- Non-compliance could be lack of testing or measurement at defined points, or coercion of subjects so intense as to adulterate survey results
- Is it research misconduct?

Research Misconduct - Examples

- Researcher falsifies informed consent forms in a study in which informed consent has been described in acute detail in research protocol approved by the IRB, even though subjects enrolled in the study were otherwise treated appropriately;
- In publication, the human subjects section describes the elaborate informed consent process, but with gross inaccuracy; IRB discovers this serious deviation, and demands that researcher abandon data;
- Study was paid for with significant federal grant funds is now worthless.
- Is it research misconduct?

Research Misconduct - Examples

- Researcher fabricates research data on 50 subjects; enrollment was reported as 100 but was actually 50 who enrolled and completed a complicated, lengthy protocol;
- The protocol had no direct benefit for those 50 subjects who actually completed the study;
- Fabricated data on 50 fictitious subjects were combined with actual data on another 50 true subjects, and are published;
- This is fabrication of data and depriving subjects of their time and trouble, with only a false promise of scientific benefit for society or any specific population
- Is this research misconduct also a human subjects violation?

Research Misconduct - Examples

- Researcher believes that human subjects data that appear to be outliers in an otherwise consistent data set were actually inaccurately measured, and so he or she "adjusts" the outlier data to what he or she believes are more correct values;
- The data are aggregated from both the true and false values, but later analysis reveals researcher falsification;
- Have subjects been cheated of the scientific benefits to society promised at enrollment?
- Is this research misconduct a violation of human subjects research standards?

Research Misconduct - Examples

- Researcher has falsified eligibility criteria and enrollment forms for subjects, so that a full complement can be enrolled quickly;
- Study is conducted with multiple subjects whose eligibility criteria/enrollment forms were falsified;
- Research misconduct inquiry process reveals this and disclosure is made to IRB, leading to an IRB finding that multiple subjects who were actually ineligible for the study were subjected to serious and harmful research interventions
- Is this research misconduct also a violation of human subjects research standards?

Research Misconduct - Examples

- Researcher enrolls subjects who are not clinically eligible for a study and either falsifies enrollment records, or creates accurate enrollment records, but in presentations to FDA and other publications of study results, represents, falsely, that the subject population was defined by certain eligibility and ineligibility criteria; and this was a demonstrably false statement, both in FDA submission and in publication of study results
- Is this FDA violation also research misconduct and a violation of human subjects research standards?

Research Misconduct – Examples

- Researcher fails to report serious and unexpected adverse events, and/or injuries to subjects that could have been avoided;
- Adverse events and/or injuries in turn were not reported in FDA submissions, and were not reported in publications;
- Publications and FDA submissions indicate, in fact, that few or no serious adverse events occurred during the study
- Is this FDA violation also research misconduct and a violation of human subjects research standards?

Research Misconduct - Issues

- When does an allegation of Research Misconduct – just a serious allegation that appears to have some real substance – also qualify as "unanticipated problem involving risks to subjects or others or any serious or continuing noncompliance" that requires prompt reporting to OHRP?
- What are confidentiality implications when an allegation of research misconduct has been reported to OHRP by the IRB, but the research misconduct proceeding (which is often a years-long process) has not been concluded?

Research Misconduct - Issues

- What are confidentiality implications when the IRB has investigated a situation that arose during a parallel research misconduct proceeding, but IRB finding and penalties long precede any conclusion of research misconduct process, and IRB makes its required report to OHRP?

Research Misconduct - Issues

- What if IRB determination in these cases differs from research misconduct findings?
- How does RIO interact with IRB? At what point in a research misconduct process does a RIO inform IRB of allegations that may be human subjects violation?
- Should research subjects be informed if and when research misconduct has been conclusively determined in a study in which the subjects participated?

Research Misconduct – Summary of "Disharmony Issues"

- Process disparities
  - how initiated
  - who initiates
  - who has burden of proof
  - what is the burden of proof
- Reporting disparities: timeline, circumstance, content
- Sanctions disparities

Research Misconduct – Summary of "Disharmony Issues"

- Confidentiality and disclosure disparities
  - Records sequestration (is there IRB access to sequestered research misconduct records?)
  - Complainants, including those who speak publicly
  - Respondents, including those who speak publicly
  - Communications to co-authors and journals (including extent of disclosure)
  - Communications to human subjects (including extent of disclosure)
  - Reporting of research misconduct/non-compliance on the web or in other public fora

- Feedback or Questions?